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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/000,433	11/30/2001	Kazuma Tomizuka	014643-012110US	9190

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/000,433	TOMIZUKA ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-9 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12/29/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed 12/19/03 has been entered. Claims 1, 2, 6-9, and 11 have been amended, and claims 3-5, 10, 12-88 have been canceled. Claims 1, 2, 6-9, and 11 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 12/19/03 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6-9, and 11 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a transgenic mouse homozygous for inactivated endogenous immunoglobulin (Ig) heavy and light chain loci, and comprising two human Ig loci including a heavy chain locus and a light chain locus, wherein the human Ig heavy chain locus is the SC20 fragment of human Chromosome 14 carried by a transchromosome, and the human Ig light chain locus is the KCo5 transgene gene integrated into the genome of said mouse, does not reasonably provide enablement for making *any* transgenic non-human mammal comprising a transchromosome having *any* fragment of human Ig heavy chain locus or

any fragment of human Ig heavy chain locus on chromosome 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In the 12/19/03 response, applicants indicated that the claims as amended are fully enabled because the specification has exemplified the generation of hCF(SC20)/Kco5 mouse. Applicants further argue that the claims are not concerned with efficiency of transchromosomal transfer but rather combining a stable, transmittable transchromosome comprising a human heavy chain locus with a transgene comprising the human light chain locus.

The arguments are fully considered but found not persuasive for reasons of record and following.

As an initial matter, the claims are not limited to the hCF(SC20)/Kco5 mouse. With respect to claim breadth, although the amended claim 1 appears to be limited to a transgenic mouse comprising a transchromosome having a centromere of human chromosome 14, the claims are in fact not limited to any particular human Ig heavy chain locus of chromosome 14. This is because "having" is an open language, thus, as long as the transchromosome carries a fragment of a chromosome that contains a centromere of human chromosome 14, it could further carries many other heavy chain loci. Moreover, even if the claim be amended to limit to a locus on chromosome 14, as indicated in the Office action of record, previous such attempts have failed as evidenced by *Tomizuka et al,* Nat. Genetics 1997 and PNAS 2000. Hence, it is unpredictable making transgenic mice with chromosomal transfer because the transchromosomes are

mitotically and meiotically unstable as taught by *Green et al* (US 2003/0093820), and it is highly unpredictable whether any random transchromosome would be stable and transmittable. Accordingly, at the time of the invention, only the transchromosome SC20 appears to be stable and capable of transmission. Therefore, it would have required undue experimentation to make a transgenic mouse comprising any transchromosome carrying any human heavy chain locus or any *IgH* locus from Chromosome 14.

With respect to the genetic background of the claimed transgenic mouse, claims read on a mouse having active endogenous Ig heavy and light chain loci. However, the specification only teaches mice having null endogenous Ig loci that could successfully make human antibodies. Given the unpredictable nature of the art, it is uncertain whether mice having endogenous Ig loci could make sufficient levels of human antibodies. And even so, they would make chimeric antibodies comprising both mouse and human sequences, and the specification fails to teach how to use the chimeric antibodies. Accordingly, the specification fails to provide an enabling disclosure to support the full scope of the claims. Therefore, for reasons of record and those set forth above, the rejection stands.

It is noted that the specification has shown by reduction to practice the generation of hSC(20)/Kco5 mouse with null endogenous Ig heavy and light chain loci. Given the unpredictable nature of the transchromosome technology, the claimed hSC(20)/Kco5 mouse may not be readily available or obtainable by a repeatable method set forth in the specification or other wise known and readily available to the

public. If it is not so obtainable or available, an enabling deposit of the mice embryo may satisfy the requirements of 35 U.S.C. 112, first paragraph.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "the SC20 transchromosome". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1, 6-8 are rejected under 35 U.S.C. 102(e) as being anticipated by *Tomizuka et al* (US 6,632,976)

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims of the present application and the cited patent (Claims 22, 25, 27-29, 32. 35, 36, 39-41, 44-52) are each drawn to a transgenic mouse comprising a foreign chromosome or fragment thereof, which is independently maintained from the mouse chromosomes, wherein the foreign chromosome comprises a human antibody gene (e.g. claim 22 of the cited patent), wherein the endogenous Ig gene is disrupted (e.g. claim 52 of the cited patent), wherein a YAC vector could also be used for inserting a foreign gene (e.g. column 2, lines 15-49).

The claims of the present application and the cited patent differ in that the instant claims require the presence of a centromere of human chromosome 14, however, the cited claims broadly encompass any human chromosome fragment, and the instant claims are not limited to Ig locus of chromosome 14. Accordingly, *Tomizuka et al* anticipates the instant claims.

Claims 1, 6-8 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. US 6,632,976 anticipates the instant claims, but has a different inventive entity, thus it is unclear who is the real inventor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1,2, 6-9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Lonberg et al* (US 5,770,429), in view of *Tomizuka et al* (Nat Genetics 1997;16:133-43 and PNAS 2000 Jan;97:722-7).

Lonberg et al teach the necessity of making humanized antibodies with a function diversity in transgeneic mice (column 1, line 52-65) capable of producing heterologous antibodies of multiple isotypes by undergoing isotype switching (column 4, lines 34-39), wherein the transgenic mice carrying human genomic sequences of human Ig heavy and light chain loci (column 29, lines 42-67), wherein the transgenic mouse line has null endogenous Ig heavy and light chain loci, and a Kco5 light chain transgene cloned into a YAC vector and integrated into the genome of the mice (e.g. example 38, particularly, paragraph bridging columns 141-142). *Lonberg et al* go on to teach that different lines of transgenic mice could have potentially different tandem array of transgene, and selecting for mice having high level human Ig expression by breeding or other art known or subsequently developed methods (column 35, lines 28-43). *Lonberg et al* do not teach using a transchromosome carrying the Ig loci.

Tomizuka et al (1997, and 2000) teach that one of the limitations of producing transgenic mouse comprising human Ig gene is the size restriction in cloning vectors, and offered a solution by introducing chromosome fragments into mouse embryonic stem (ES) cells via microcell-mediated chromosome transfer (MMCT) and viable chimaeric mice were produced from them. *Tomizuka et al* teach that serum concentration of human Igs were several fold higher in transgenic mice carrying a transchromosome comprising a human heavy chain locus hCF(2-w23) compared to those of YAC transgenic mice (1997, page 138). They teach that transferred chromosomes were stably retained, and human genes, including immunoglobulin (Ig) kappa, heavy, lambda genes, were expressed in proper tissue-specific manner in adult chimaeric tissues. In the case of a human chromosome (hChr.) 2-derived fragment, it was found to be transmitted to the offspring through the germline. They suggest that MMCT allows for introduction of very large amounts of foreign genetic material into mice. This novel procedure will facilitate the functional analyses of human genomes in vivo. In *Tomizuka et al* 1997 publication, the chromosome 14 fragment could not be stably maintained, whereas in the *Tomizuka et al* 2000 publication, the SF20 fragment of chromosome 14 is stable and transmittable.

Evidently, it is well known in the art using transgenic mice carrying human Ig heavy and light chain loci for production of human antibodies, and such could be made by varies technologies such as YAC cloning vector and transchromosome carrier, it is also well known in the art that a array of transgenic mice with different genotype and phenotype could be made by cross breeding the available transgenics. Accordingly, it

would have been obvious to one of ordinary skill in the art at the time the invention was made to breed the mice as taught by *Lonberg et al,* and *Tomizuka et al et al*, to produce a new line of mice expressing different antibody isotope or diversity, or obtaining a higher levels of antibody production with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the crossbreeding would facilitate the production of transgenic mice variety as well as higher amount of antibodies. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6-8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22, 25, 27-29, 32. 35, 36, 39-41, 44-52 of U.S. Patent No. 6,632,976. Although the conflicting claims are not

identical, they are not patentably distinct from each other because the claims of the cited patent encompass instant claims.

The claims of the present application and the cited patent are each drawn to a transgenic mouse comprising a foreign chromosome or fragment thereof, which is independently maintained from the mouse chromosomes, wherein the foreign chromosome comprises a human antibody gene (e.g. claim 22 of the cited patent), wherein the endogenous Ig gene is disrupted (e.g. claim 52 of the cited patent), wherein a YAC vector could be used for inserting a foreign gene (e.g. column 2, lines 15-49).

The claims of the present application and the cited patent differ in that the instant claims require the presence of a centromere of human chromosome 14, however, the cited claims broadly encompass any human chromosome fragment, and the instant claims are not limiting to Ig locus of chromosome 14. Accordingly, the claimed mice in the present application and the cited patent are obvious variants.

Therefore, the inventions as claimed are co-extensive.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
March 22, 2004